14th ASEICA INTERNATIONAL CONGRESS
Spanish Society for Cancer Research

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ASOCIACIÓN ESPAÑOLA DE INVESTIGACIÓN SOBRE EL CANCER

STEM CELL REPROGRAMMING AS A DRIVER OF CANCER: IMPLICATIONS IN ITS DEVELOPMENT AND TREATMENT

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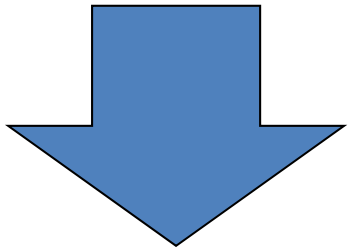
Current model of cancer

-Homogenous mode of action for oncogenes within cancer cells.

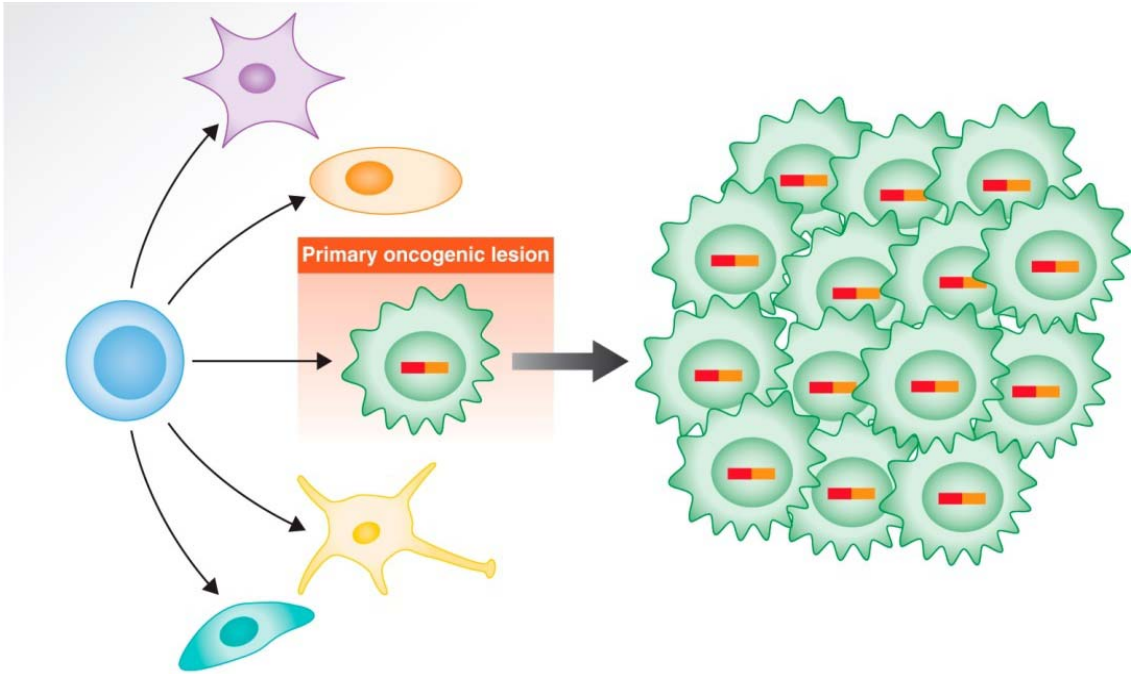
-Brief inactivation of oncogenes can cause cancer remission in model systems.

-However, unfortunately, the therapies based on this cancer model fail to eradicate tumours in humans.



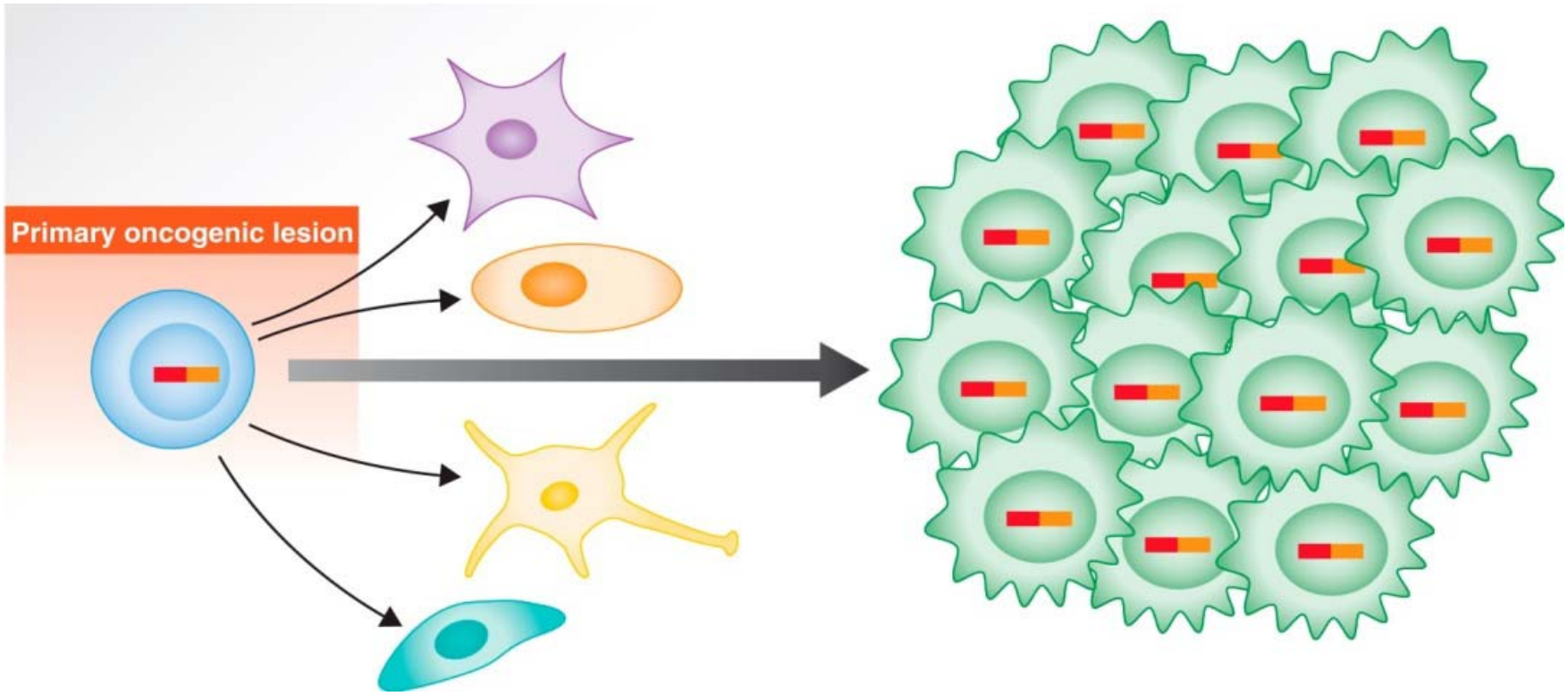
Do the oncogenes have a mode of action that is not homogeneous throughout the cancer cell population?

Classical model for the role of human cancer gene defects in tumour cell fate specification



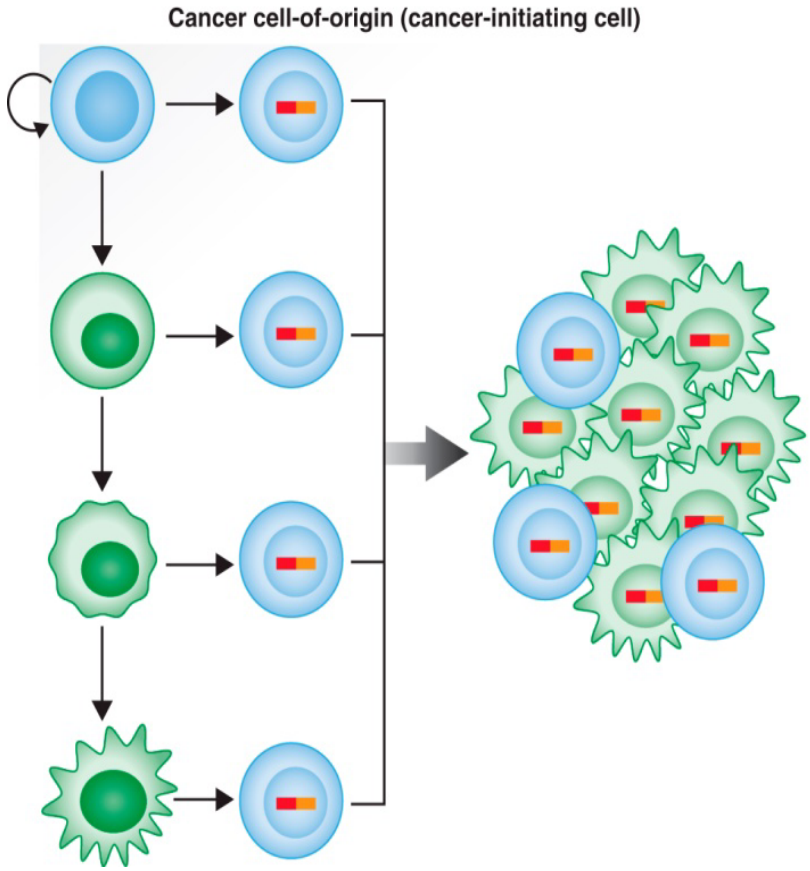
Traditionally, the human cancer genetic defects have been thought to act on cells already committed to a differentiation program, in such a way that the tumoural phenotype is derived from that of the initial differentiated target cell

Alternative model for the role of human cancer gene defects in tumour cell fate specification



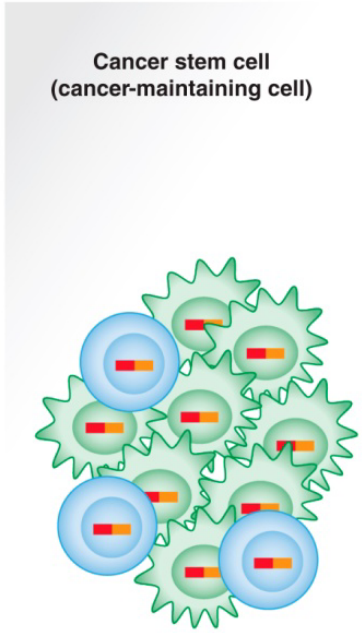
Alternative view in which the oncogenic lesion acts on stem/progenitor cells by imposing a given, oncogene-specific, tumour-differentiated cell fate.

The nature of the cancer cell-of-origin



Cancer cell-of-origin (or cancer-initiating cell): the cell where the first genetic lesion linked to the development of the tumour takes place. It might be located anywhere within the physiological differentiation pathway.
It does not need to have any phenotypic relationship with the final phenotype of the tumour cells (either stem or differentiated).

Cancer stem cell theory



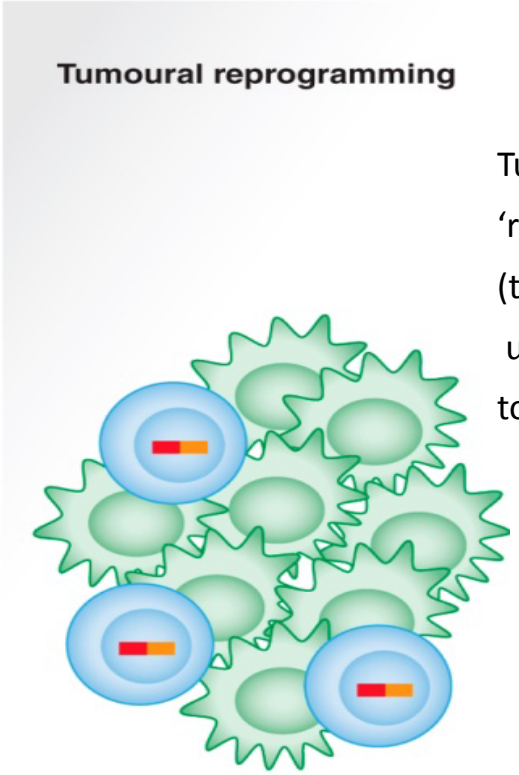
CSC (cancer-maintaining cell): those cells that have the capacity to regenerate all the cellular diversity of the tumour.

They retain broad self-renewal potential and differentiation potential.

They arise initially from the cancer cell-of-origin, and then they can self-propagate.

The CSC hypothesis is in good agreement with the interpretation of oncogenesis presented in slide 4.

The tumoural stem cell reprogramming hypothesis

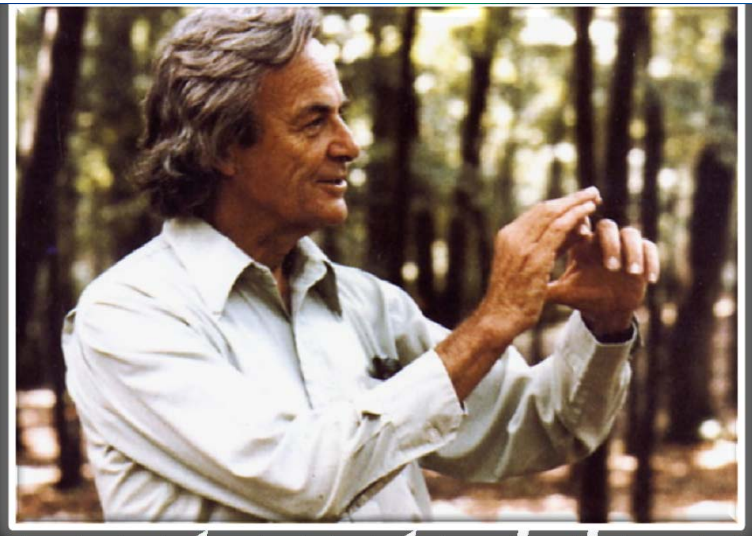


Tumoural reprogramming: the process by which the initial oncogenic lesion(s) can 'reset' the epigenetic and/or transcriptome status of an initially healthy cell (the cancer cell-of-origin), therefore establishing a new, pathological differentiation program ultimately leading to cancer development, where the oncogenic lesion(s) does not need to be present anymore once the initial cancer fate-inducing change has taken place.

Vicente-Dueñas *et al. The EMBO Journal* 2013

In vivo experimental model of tumoral stem cell reprogramming

To be able to demonstrate this lack of homogeneity in the mode of action of oncogenes throughout the biological history of the tumor, it would be necessary to dissect and isolate the function that the oncogene is playing at the earliest stages of the disease, at the level of the cell-of-origin

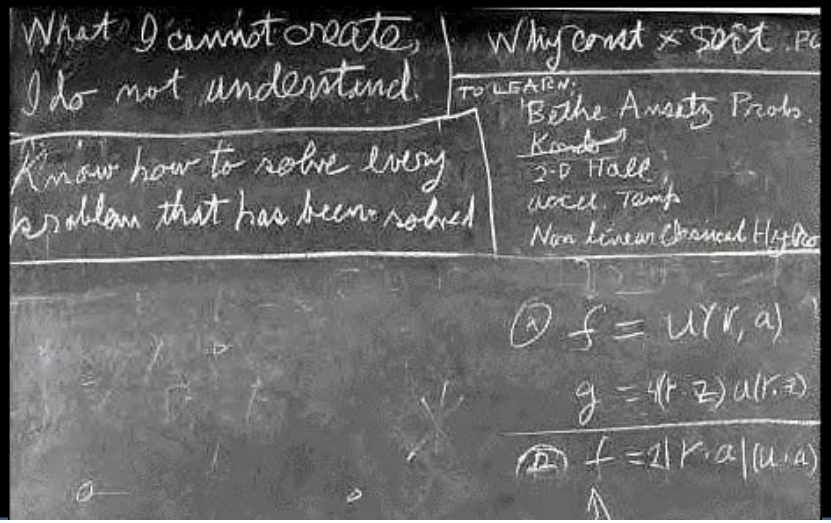


"What I cannot create, I do not understand"

Richard P. Feynman

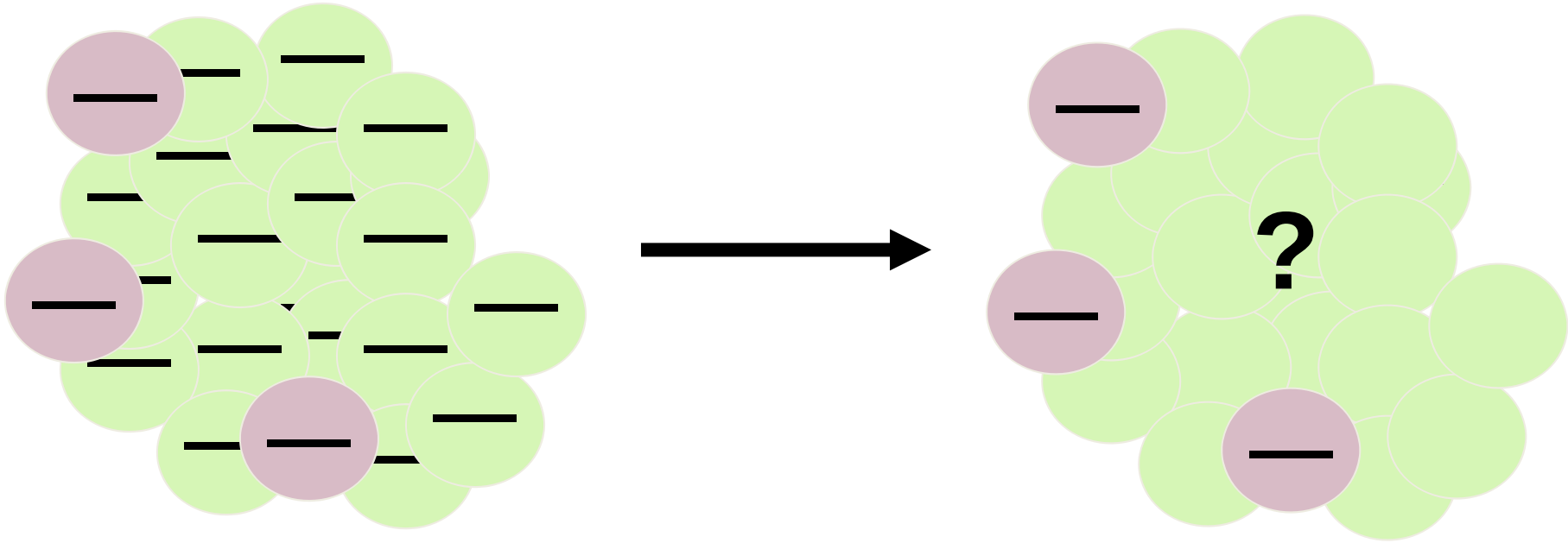
Nobel Prize in Physics 1965

Written on his blackboard at time of his death, in 1988



Human Cancer tissue

In vivo experimental model of tumoural stem cell reprogramming



Genetic defect is present in both CSC and differentiated tumor cells

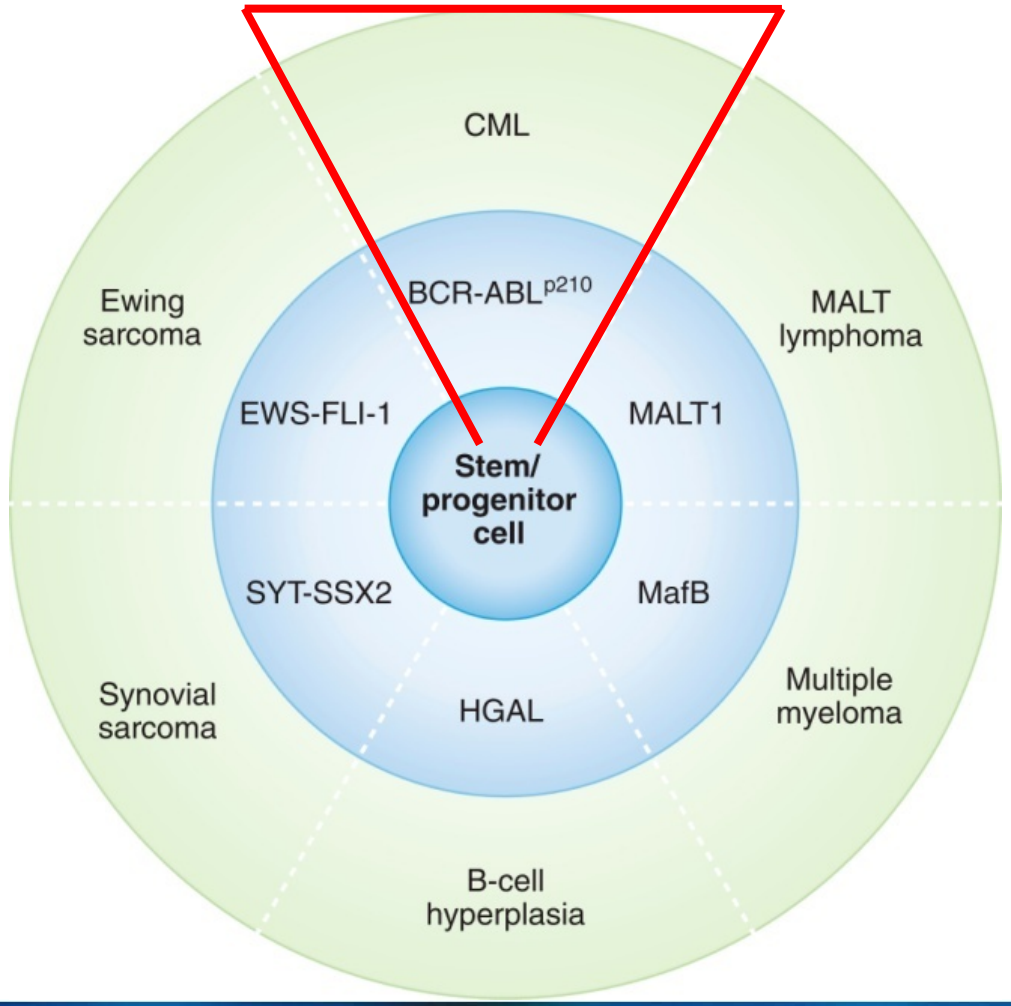
Genetic defect is only present in CSC

Might cancer stem cells initially arise thorugh a reprogramming-like mechanism?

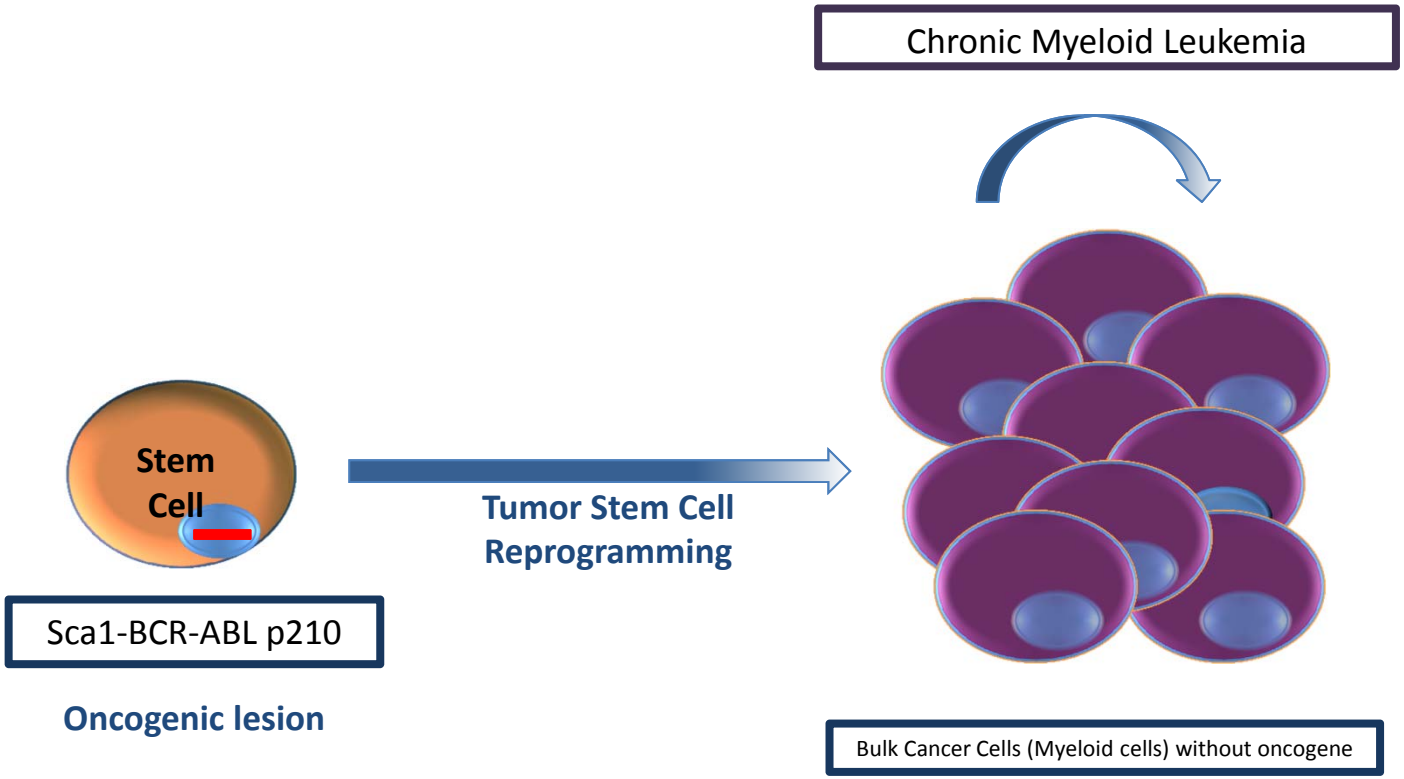
To be able to demonstrate this lack of homogeneity in the mode of actions of oncogenes throughout the biological history of the tumour.

This still unexplored possibility would have major implications for our understanding of the genesis and treatment of cancer

Reprogramming in malignancies originated from stem cells



Tumoral stem cell reprogramming in malignancies supposed to originate in HSC



EMBO J. 28(1):8-20 (2009).
Cell Cycle 8:1314-1318 (2009)
N Engl J Med. 360(3):297-299 (2009)

Tumoral stem cell reprogramming in malignancies supposed to originated HSC

1- Proof of principle experiment

2- Chronic myeloid **leukemia** (CML) **stem cells are not oncogene addicted** and the therapies that biochemically target BCR-ABL do not eliminate them (CML stem cells).

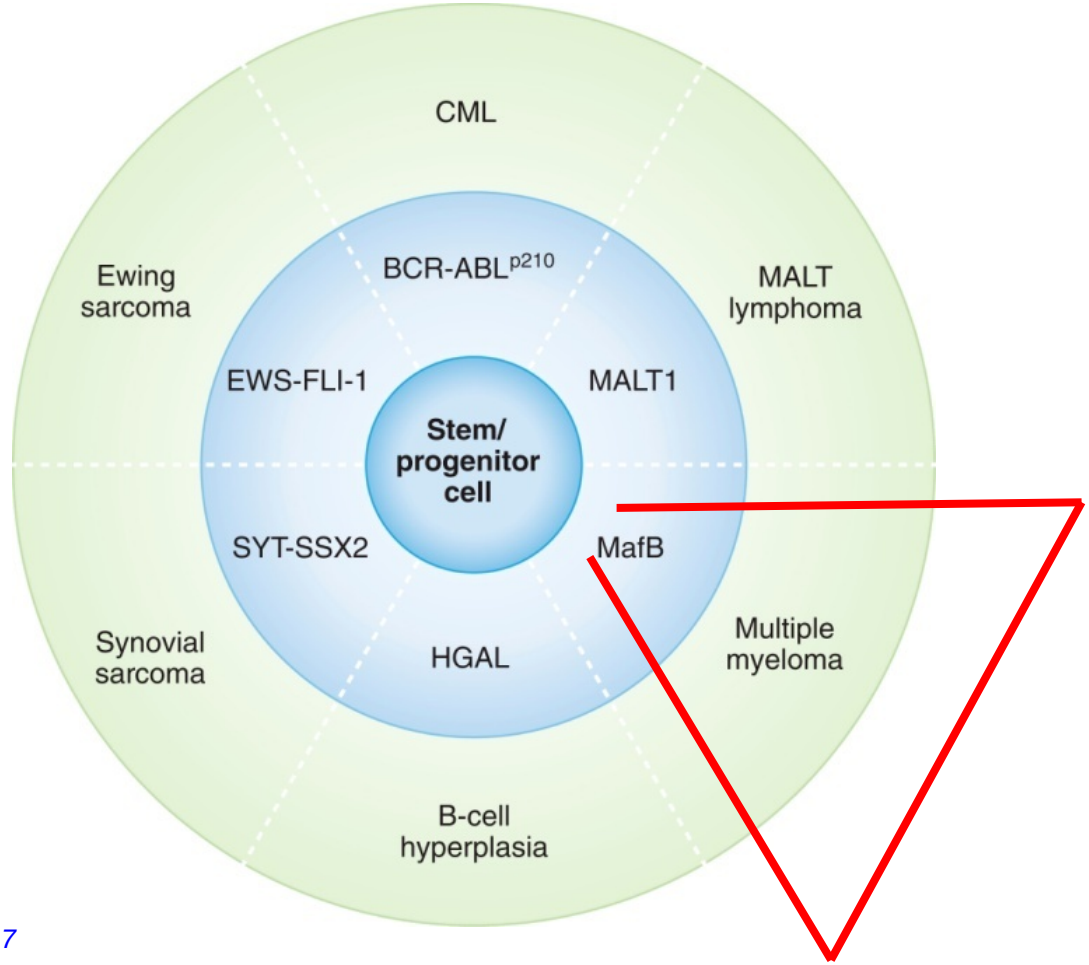
3-First animal model aniticipating human clinical results in the CSC field

4-Results were confirmed in human patients two years later

EMBO J. *28(1):8-20 (2009).*
Cell Cycle *8:1314-1318 (2009)*
N Engl J Med. *360(3):297-299 (2009)*

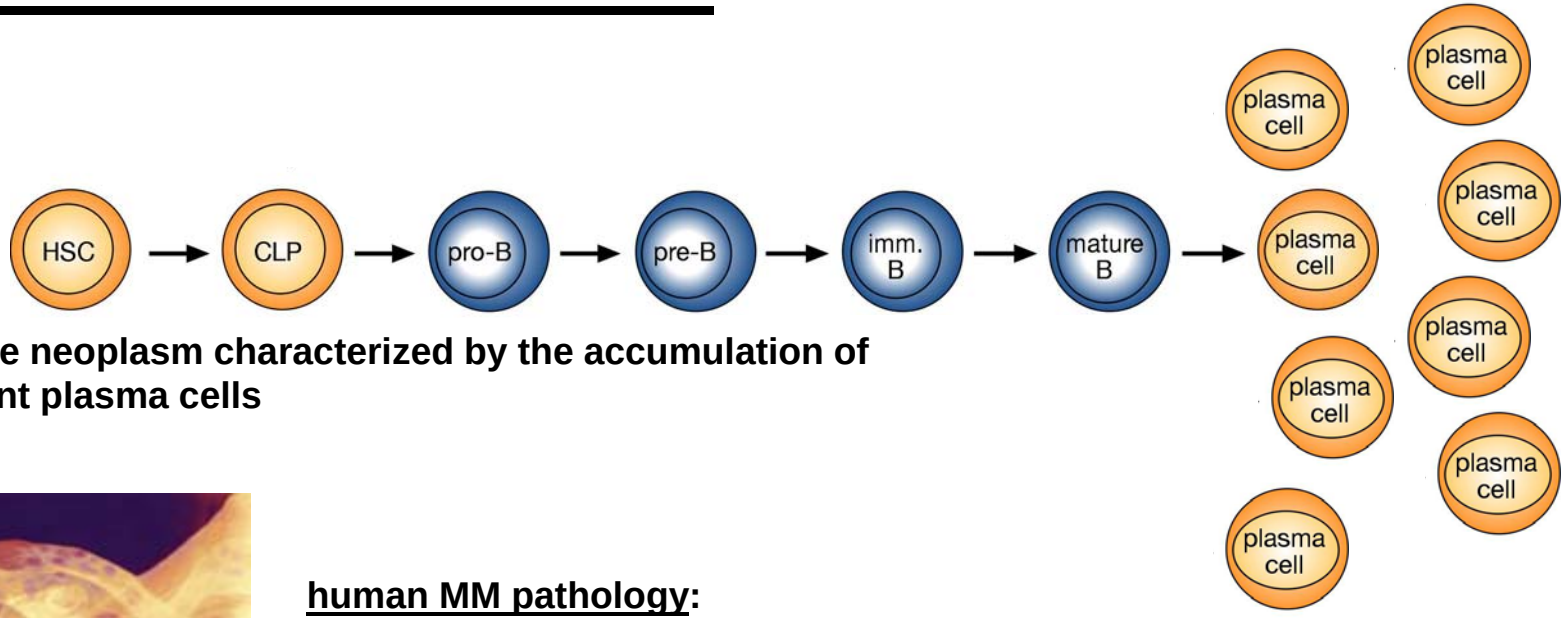
Can this hypothesis be extrapolated to other malignancies?

Contribution of MafB to multiple myeloma biology?

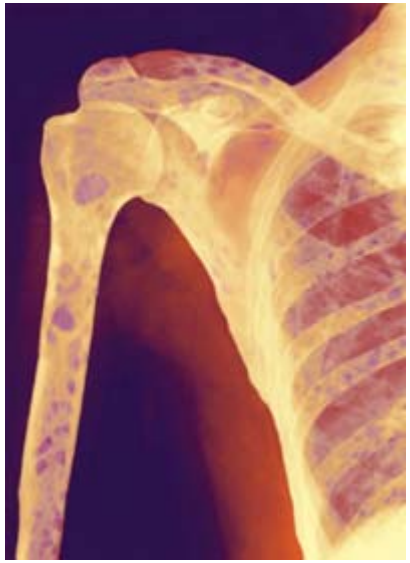


Cell Cycle. 2013;12(1):122-32.
EMBO J. 2012 Sep 12;31(18):3704-17

Human multiple myeloma



Incurable neoplasm characterized by the accumulation of malignant plasma cells



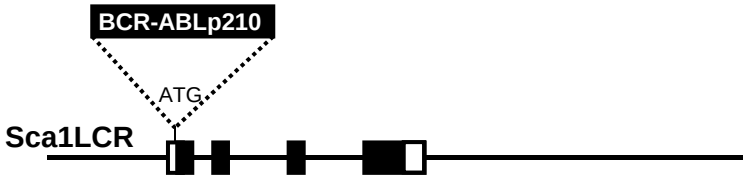
<u>human MM pathology</u>:

- **Bone marrow plasmacytosis.**
- **Serum accumulation of monoclonal immunoglobulin.**
- **Amyloid Deposits.**
- **Kidney damage.**
- **Osteolytic lesions.**
- **Bone marrow failure.**

Cancer Cell-of-Origin and Reprogramming in Multiple Myeloma

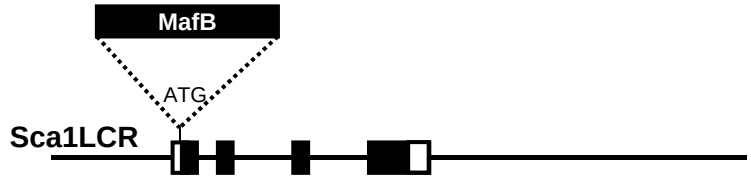
Generation of Sca1-MafB mice

Accepted Stem Cell-based tumor:
Chronic Myeloid Leukemia



EMBO J (2009) 28:8-20; *Cell Cycle* (2009) 8:1314-1318

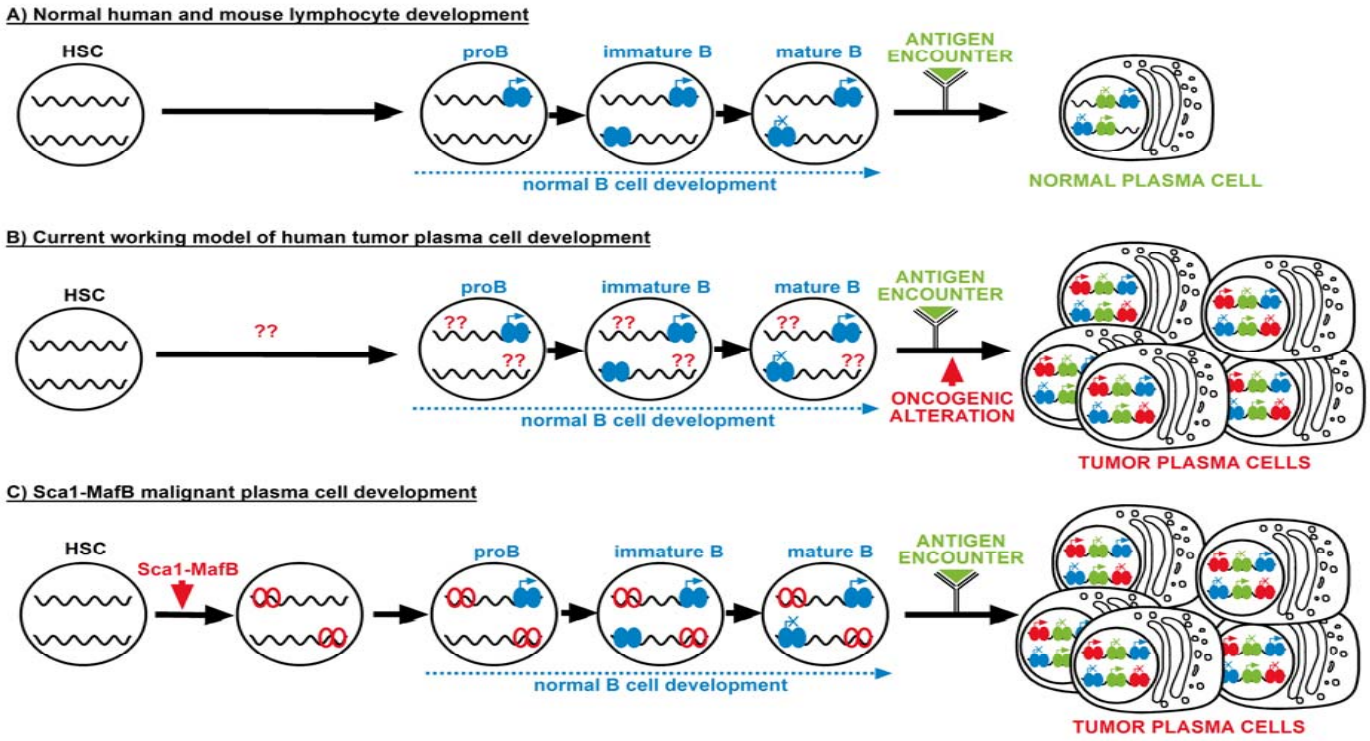
Accepted Differentiated Cell-based tumor:
Multiple Myeloma



EMBO J. *31(18):3704-17 (2012);* ***Cell Cycle*** *11(20):3896-900 (2012)*

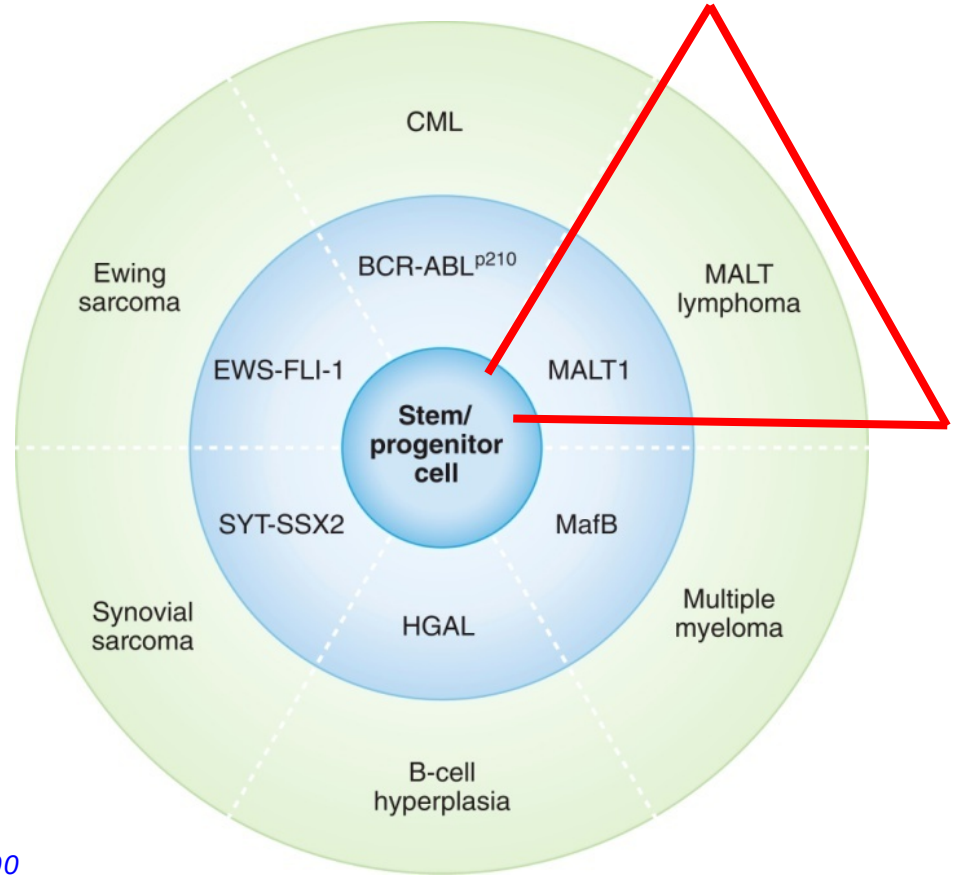
Human MM disease has not been modelled in mice when human oncogenes have been targeted to the mouse B-cell compartment

Multiple myeloma as a result of tumoral stem cell reprogramming



The results demonstrate that HS/P-Cs can be reprogrammed to terminally differentiated tumor plasma cells by a defined factor (MafB).

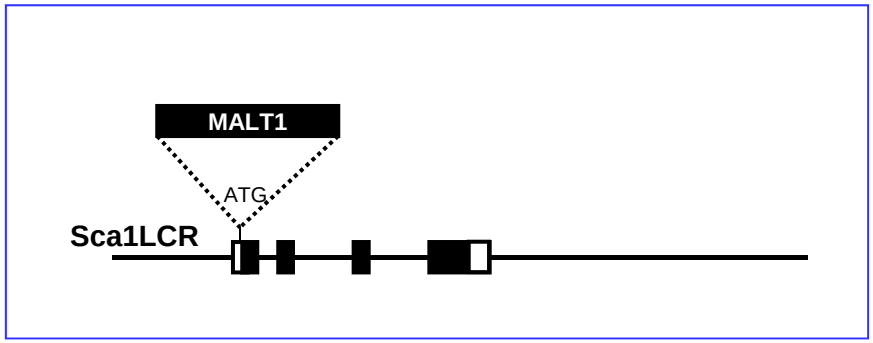
Contribution of MALT1 to lymphoma biology?



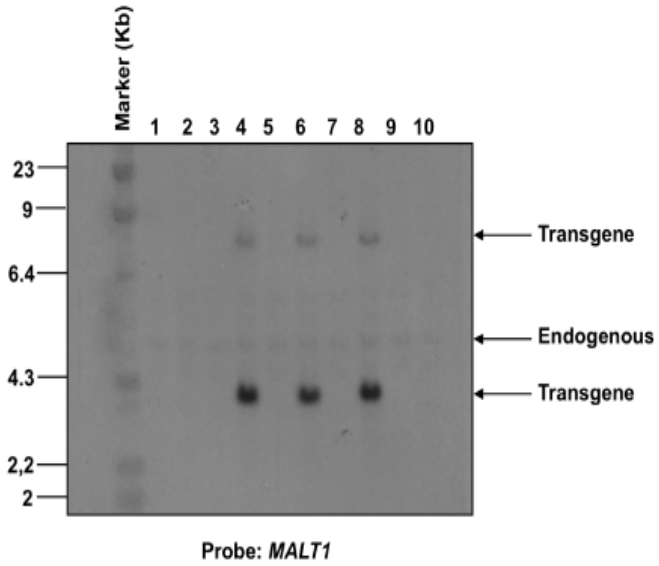
Nat Commun. 2013;4:1338
Cell Cycle. 2013;12(1):122-32.
Cell Cycle. 2012;11(20):3896-900
EMBO J. 2012 Sep 12;31(18):3704-17
Proc Natl Acad Sci U S A. 2012;109(26):10534-9

Cancer Cell-of-Origin and Reprogramming in MALT1 lymphoma

Generation of Sca1-MALT1 mice



Proc Natl Acad Sci U S A. 2012 Jun 26;109(26):10534-9



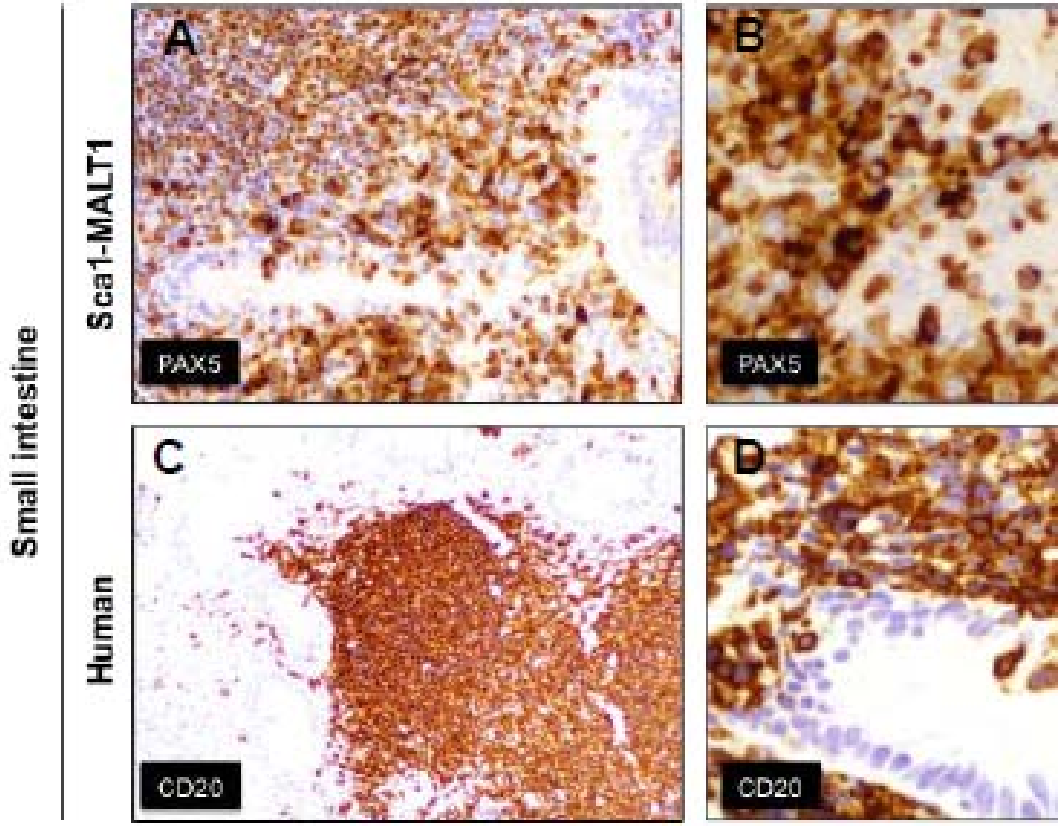
Human MALT disease has not been modelled in mice when human oncogenes have been targeted to the mouse B-cell compartment

Typical histopathological picture:

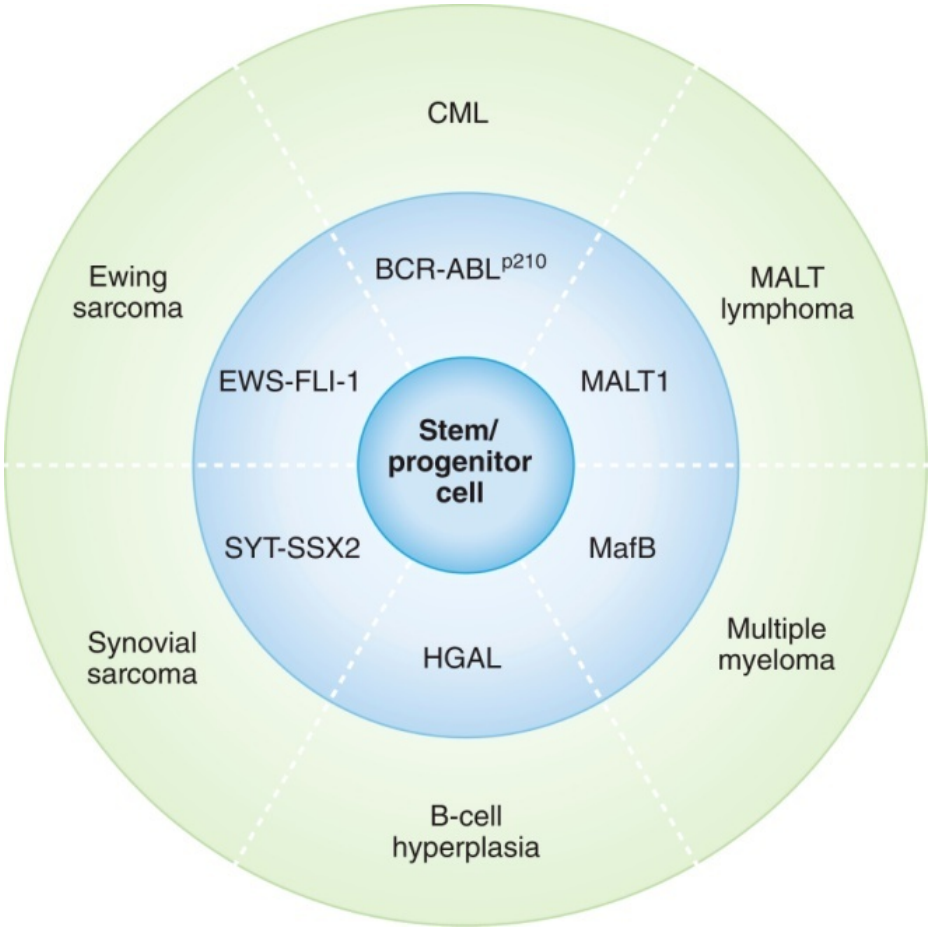
Tumors involved multiple extranodal sites, including the spleen, small intestine, salivary glands, kidneys, lungs, liver, stomach and ocular adnexa.

In the epithelial tissues, the cells infiltrated the epithelium and formed lymphoepithelial lesions.

MALT1 lymphoma as a result of tumoral stem cell reprogramming

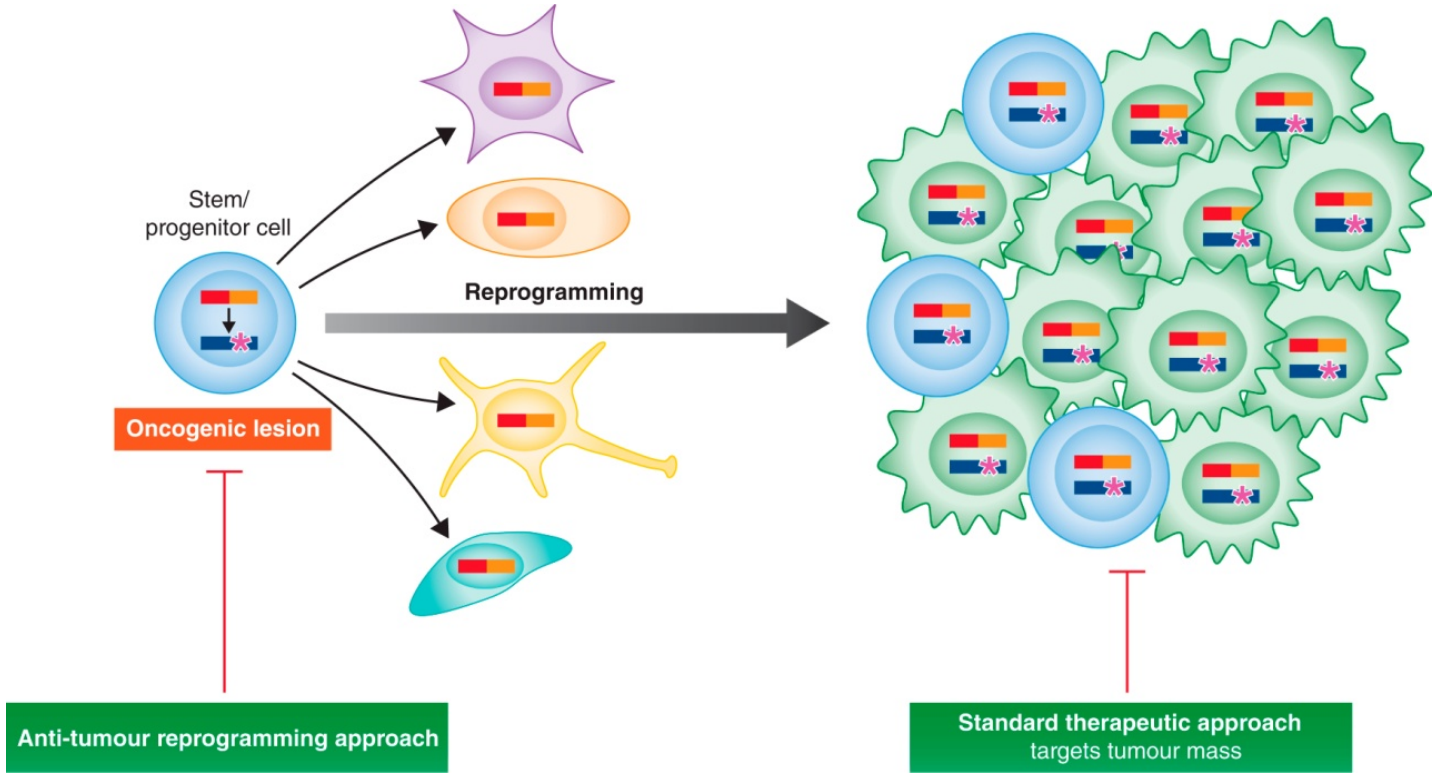


Intestinal human MALT lymphomas and human-like mouse MALT lymphomas showed similar histopathological pictures including typical lymphoepithelial lesions



Cell Cycle. 2013;12(1):122-32.
EMBO J. 2012 Sep 12;31(18):3704-17

Tumour stem cell reprogramming and therapeutic implications



Reprogramming the cancer epigenome to an alternative lineage cell fate, non-tumoral fate, losing their malignancy?

Tumour stem cell reprogramming largely relies on epigenetic modifications. These, unlike genetic changes, can be erased, manipulated, and reinitiated, therefore implying that anti-tumour reprogramming strategies can provide a new window of opportunity to interfere with the cancer fate-inducing change.

What lies ahead?

Stem cell reprogramming (where the maintenance of oncogene expression is not critical for the generation of differentiated tumor cells) seems to be a common intrinsic mechanism for many type of cancers, and this should change our understanding of the means by which “hallmark cancer capabilities” are acquired.

This conceptualization of tumour reprogramming by oncogenes will change the way we investigate and treat cancer in the years to come:

1- These discoveries introduce a new perspective on oncogenic transformation: certain oncogenes may act as “passengers” to reprogram tissue-specific stem/progenitors cells into a malignant cancer stem cell state.

2- This discovery will also force us to explore and answer fundamental questions in cancer biology, such as how cells acquire and maintain their tumour differentiation states (oncogenes work as a new type of gene-target cell interaction in which oncogene exposure targets the epigenome to induce cancer development).

3- To add new layers of complexity, the effect of such epigenetic reprogramming may remain dormant until engaged in response to later adult events (genetics and/or environmental).

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